DEVICE AND METHOD FOR THE CESSATION OF SMOKING

BACKGROUND OF THE INVENTION

Field of the Invention

The field of the present invention is pharmacology. More specifically, the invention relates to smoking cessation methods and aids that provide a non-irritating form of nicotine to the user as well as the oral and tactile stimulation of smoking.

Summary of the Related Art

Cigarette smoking is the leading cause of preventable disease and death in the United States. Each year, over 400,000 adults die from tobacco-related diseases (A Report of the Surgeon General, Rockville, MD: Public Health Service (2000)). In addition to health risks facing smokers themselves, the annoyance and risks of second-hand smoke are receiving increased attention. Although airlines, workplaces, and restaurants often ban smoking, almost 88% of non-smokers have detectable blood levels of nicotine metabolites (Morbidity and Mortality Weekly, November 5, 1999). Environmental tobacco smoke remains a preventable health hazard for smokers' co-workers and family members (A Report of the Surgeon General, Rockville, MD: Public Health Service (2000)).

Unfortunately, 48 million adults in the United States, 24.7% of the population, continue to smoke. Despite public health initiatives, smoking prevalence among adults has not changed significantly throughout the 1990's (Morbidity and Mortality Weekly, November 5, 1999). Although most smokers in the United States wish to stop smoking, and over one third of them attempt to give up smoking each year, only about 2.5% succeed (A Report of the Surgeon General, Rockville, MD: Public Health Service (2000)).

Various techniques have been advanced to aid smoking cessation. The five major pharmacotherapies for treating tobacco dependence are nicotine gum (see, *e.g.*, U.S. Patent No. 3,845,217); nicotine transdermal patch (see, *e.g.*, U.S. Patent No. 4,915,950); nicotine nasal spray (see, *e.g.*, AU 664 41); nicotine inhaler (see, *e.g.*, U.S. Patent Nos. 4,920,989 and 4,953,572); and sustained-release bupropion hydrochloride (see, *e.g.*, Jorenby et al., N. Engl. J. Med., **340**:685-91(1999)). Other examples of smoking cessation aids include nicotine nose drops (see, *e.g.*, U.S. Patent No. 4,579,858); nicotine lozenges (see, e.g., U.S. Patent Nos. 4,806,35 and 5,549,906); smoke-free cigarettes (see, *e.g.*, U.S. Patent Nos. 4,284,089, 4,676,259, 4,736,755, 4,813,437, 5,284,163, and 6,041,789); compositions comprising nicotine metabolites (see, *e.g.* U.S. Patent No. 5,869,505); and drinkable nicotine solutions (see, *e.g.*, WO 99/55371).

Studies have shown that smokers using nicotine gum, patch, nasal spray, inhaled nicotine, or nicotine sublingual tablets are about 1.5 to 2 times more likely to stop smoking than smokers using no cessation aid, and evidence suggests that bupropion may be even more effective (see, Silagy et al., Cochrane Database Syst. Rev., No. 2, p.CD000146 (2000)). However, each of the existing smoking cessation aids has drawbacks, and none has proven fully effective.

For example, nicotine gum and lozenges can cause high localized nicotine concentration in the mouth, which tastes unappealing, and the gum may be difficult to chew. In addition, chewing gum or eating lozenges may appear unprofessional. Nicotine patches may irritate the skin, and some smokers are dissatisfied with the lack of rapid nicotine absorption from the patch. Nicotine nasal sprays may irritate the nose and throat. More importantly, none of these smoking cessation aids simulates the tactile sensations or hand-to-mouth behaviors that form an integral part of the smoker's addiction.

Studies have shown that sensory aspects affect smoking behavior and cigarette cravings as much as nicotine intake does. Indeed, smokers attempting to give up cigarettes have complained that, aside from experiencing nicotine withdrawal, they miss the sensations and hand-to-mouth behaviors associated with smoking (see, Rose, Ann. Rev. Med., **47**:493-507 (1996)). In a study prepared for the American Lung Association, 41% of smokers reported that their most recent attempt to stop smoking was unsuccessful because they missed having something to hold or to do with their hands (Smoking Cessation Study, Yankelovich Partners, July 27, 1998). Cigarette smoking involves a hand-to-mouth ritual that may be repeated over 70,000 times per year. Since smoking cessation requires giving up a highly ingrained habitual motion as well as giving up nicotine, an effective smoking cessation aid should address the behavioral components of smoking as well as providing nicotine replacement therapy. A smoking cessation aid should give the smoker the comfort of an oral and tactile ritual, while at the same time supplying nicotine. However, a smoking cessation device that is too similar to a conventional cigarette and provides oral sensations and tactile stimuli that too closely mimic tobacco smoking may not be ideal. A smoker using such a device might find it too easy to relapse into cigarette smoking (see, *e.g.*, Schneider et al., Addiction, **91**:1293-1306 (1996)). Thus, a smoking cessation aid that provides the synergistic combination of nicotine plus oral and tactile stimuli, while not too closely approximating a conventional tobacco cigarette, seems most desirable.

Among the existing smoking cessation aids, patches provide no oral or tactile stimulus, gum, lozenges, and drinkable solutions stimulate only the mouth, and nasal sprays stimulate only the airways. These aids lack the important synergistic combination of nicotine, oral stimulation, and hand-to-mouth behaviors that smokers desire.

Some existing smoking cessation aids, such as nicotine inhalers and various smoke-free cigarettes, do provide nicotine as well as some behavioral aspects of smoking. However, these products have major drawbacks. For example, U.S. Pat. No. 4,953,572 (Rose et al.) discloses a nicotine aerosol spray designed to simulate the sensations of inhaling tobacco smoke. The spray may be administered through inhalation from a hand-held nebulizer. However, the nicotine dose of the spray, which is limited by the volatility of the inhaler's nicotine base at room temperature, is low compared to that of tobacco smoke, and thus may be insufficient for many smokers. Additionally, such a spray may irritate the oral cavity.

U.S. Patent No. 5,284,163 (Knudsen et al.) discloses a smoke-free cigarette substitute comprising a nicotine granulate in a tubular sleeve. The end of the sleeve contains a gum plug, which is bitten off and held in the mouth as chewing gum. When a person draws on the cigarette, nicotine granulate is pulled into the mouth and can be chewed into the gum, thus dispensing nicotine into the oral cavity. This product may possess the drawbacks of nicotine chewing gum described above. Also, as with any smoke-free cigarette, using it may approximate the behavioral aspects of smoking so closely that smoking cessation becomes more difficult.

U.S. Patent Nos. 4,284,089 and 4,813,437 (Ray) disclose non-pyrolytic devices shaped like ordinary cigarettes and containing porous polymer plugs holding volatile liquid nicotine. Drawing on the device delivers nicotine vapors to a person's lungs. However, these devices are unable to deliver sufficient uniform doses of nicotine. Additionally, the vaporizable nicotine tastes unpleasant and is unstable, such that the devices have a very short shelf life.

U.S. Patent No. 6,041,789 (Bankert et al.) addresses some of these problems with a non-pyrolytic cigarette substitute that delivers a nicotine-simulating vapor mixture with a cigarette-like taste and aroma. Instead of vaporizable nicotine, the device contains a volatile

nicotinomimetic agonist and volatile palatability enhancing agents. However, this device does not actually deliver nicotine. Additionally, the cigarette-like structure, taste, and aroma may make the device so similar to a conventional cigarette that smokers using it as a cessation aid are likely to relapse.

Japanese Patent No. 02190178 (Akimichi et al.) discloses a smoke-free tobacco "perfume solution" that may be vaporized and administered through a "tubular flexible casing." However, the solution may present health risks due to the carcinogens and irritating particulates contained in tobacco. Additionally, as with other smoke-free cigarettes, using the device may approximate the actual tastes, smells, and motions of cigarette smoking so closely that smoking cessation is made more difficult.

U.S. Patent No. 5,293,883 (Edwards) discloses a non-pyrolytic cigarette containing two tobacco-filled chambers, which house unburned and pre-burned tobacco, and a mouth filter that holds nicotine-filled ampules that release pure liquid nicotine into a person's mouth when the person breaks them open by biting or manually crushing the mouth filter. This device provides nicotine and a cigarette-like taste, but it may suffer from the drawbacks of liquid nicotine described above. Additionally, as discussed above, the device presents the health hazards of tobacco and may make smoking cessation more difficult by too closely approximating actual tobacco cigarettes.

Thus, a continuing need exists for new and improved smoking cessation aids to help reduce the ongoing public health hazards associated with cigarette smoking and second-hand smoke. Particularly needed is a smoking cessation aid that synergistically provides an easily controllable nicotine dose in a non-irritating form along with a delivery device that supplies the

oral and tactile stimulation that smokers crave, without too closely approximating actual cigarette smoking.

SUMMARY OF THE INVENTION

The present invention solves the foregoing problems by providing a smoking cessation aid that delivers nicotine in non-irritating solution form and offers the oral and tactile stimulation that smokers crave. Drawing a nicotine solution through the device and into the mouth is similar to the accustomed hand-to-mouth behavior of smoking. However, because the nicotine is delivered as a solution rather than as inhaled vapors, using the present smoking cessation aid is different enough from actual smoking that behavioral similarities should not encourage smokers to relapse. Nicotine delivered as a solution also does not irritate the oral cavity as do inhaled vapors from a nicotine spray.

Accordingly, in one aspect, the invention provides an oral nicotine delivery device comprising a tubular chamber, a nicotine granulate contained within the chamber, and a retainer in the chamber. The chamber has a first end suitable for taking in a liquid from an external source and a second end suitable for oral application of suction. The retainer prevents release of the nicotine granulate and liquid from the first end of the chamber. When oral suction is applied to the second end of the chamber, liquid enters the chamber from the external source through the first end of the chamber, and then the liquid and the nicotine are delivered through the second end of the chamber. As used herein, the term "comprises" means "includes, but is not limited to."

In one embodiment, the tubular chamber of the device approximates the size and shape of a conventional cigarette. In another embodiment, the tubular chamber approximates the size and shape of a conventional drinking straw.

In some embodiments, the retainer is fixed proximal to the first end of the chamber. In other embodiments, the retainer is transportable toward the second end of the chamber with the nicotine granulate and the liquid when suction is applied to the second end of the chamber.

In some embodiments, the nicotine granulate comprises coated particles of powdered nicotine. In particular embodiments, the nicotine particles are coated to enhance palatability. In some embodiments, the nicotine granulate comprises particles of powdered nicotine that are incorporated in spheres comprising at least one material selected from the group consisting of sugar, starch, acacia, sodium alginate, carbomer, cellulose, dextrotes, ethyl cellulose, methyl cellulose, and povidone.

In another embodiment, the tubular chamber contains from about 1 milligram to about 40 milligrams of nicotine. In yet another embodiment, the tubular chamber contains from about 4 milligrams to about 12 milligrams of nicotine. The nicotine is preferably selected from the group consisting of levo nicotine, dextro nicotine, racemic mixtures thereof, and pharmaceutically acceptable salt forms thereof.

In some embodiments, a solution of nicotine is formed when the liquid enters the chamber and contacts the nicotine. In particular embodiments, the solution is a suspension.

In another aspect, the invention provides a method for reducing the incidence of tobacco smoking by a person. The method comprises orally administering nicotine to the person using the device according to the previous aspect of the invention. The person applies oral suction to the second end of the chamber, such that the liquid enters the chamber from the external source

through the first end of the chamber. The liquid and the nicotine are then delivered through the second end of the chamber into the mouth of the person.

In one embodiment of the method, a single dose of nicotine administered to the person is from about 1 milligram to about 40 milligrams of nicotine. In a particular embodiment, the dose administered is from about 4 milligrams to about 12 milligrams of nicotine. In a preferred embodiment, the total daily dose of nicotine administered to the person is from about 4 milligrams to about 144 milligrams of nicotine. In some embodiments, the blood level of nicotine in the person after administration of the nicotine is at least about 5 nanograms of nicotine per 1 milliliter of blood. In some preferred embodiments, the blood level of nicotine in the person after administration of the nicotine is from about 10 nanograms to about 50 nanograms of nicotine per 1 milliliter of blood.

In some embodiments of the method, a solution of nicotine is formed when the liquid enters the chamber and contacts the nicotine. In particular embodiments, the solution has an acidic pH.

In another aspect, the invention provides an oral nicotine delivery device comprising a tubular chamber, a nicotine solution contained within the chamber, and a retainer. The chamber has a first end suitable for taking in a liquid or a gas from an external source and a second end suitable for oral application of suction. The retainer is for preventing release of the nicotine solution from the first end of the chamber. The nicotine solution is delivered through the second end of the chamber when oral suction is applied to the second end of the chamber.

In some embodiments of the device of the invention, a liquid enters the chamber from an external source through the first end of the chamber when oral suction is applied to the second

end of the chamber. The liquid and the nicotine solution are then delivered from the device through the second end of the chamber.

In other embodiments, a gas enters the chamber from an external source through the first end of the chamber when oral suction is applied to the second end of the chamber. The nicotine solution is then delivered from the device through the second end of the chamber.

In some embodiments, the tubular chamber approximates the size and shape of a conventional cigarette. In alternative embodiments, the tubular chamber approximates the size and shape of a conventional drinking straw.

In some preferred embodiments, the retainer is transportable toward the second end of the chamber with the nicotine solution when suction is applied to the second end of the chamber.

In a particular embodiment, the nicotine solution is a nicotine suspension. In a preferred embodiment, the nicotine suspension comprises a nicotine granulate. In some embodiments, the nicotine granulate comprises coated particles of powdered nicotine, and in some preferred embodiments, the nicotine particles are coated to enhance palatability. In some embodiments, the nicotine granulate comprises particles of powdered nicotine that are incorporated in spheres comprising at least one material selected from the group consisting of sugar, starch, acacia, sodium alginate, carbomer, cellulose, dextrotes, ethyl cellulose, methyl cellulose, and povidone.

In a preferred embodiment, the nicotine solution contains from about 1 milligram to about 40 milligrams of nicotine. In a particular embodiment, the nicotine solution contains from about 4 milligrams to about 12 milligrams of nicotine. In a particular embodiment, the chamber contains from about 1 milliliter to about 5 milliliters of the nicotine solution. The nicotine in the nicotine solution is preferably selected from the group consisting of levo nicotine, dextro nicotine, racemic mixtures thereof, and pharmaceutically acceptable salts thereof. In some

embodiments, the nicotine solution has an acidic pH. In some embodiments, the nicotine solution further comprises a flavoring.

In yet another aspect, the invention provides a method for reducing the incidence of tobacco smoking by a person. The method comprises orally administering nicotine to the person using the device according to the previous aspect of the invention. The person applies oral suction to the second end of the chamber, such that the nicotine solution is delivered from the chamber through the second end of the chamber into the mouth of the person.

In some preferred embodiments of this aspect of the invention, a single dose of nicotine administered to the person is from about 1 milligram to about 40 milligrams of nicotine. In a particular embodiment, the single dose administered is from about 4 milligrams to about 12 milligrams of nicotine. In some preferred embodiments, the total daily dose of nicotine administered to the person is from about 4 milligrams to about 144 milligrams of nicotine. In some embodiments, the blood level of nicotine in the person after administration of the nicotine solution is at least about 5 nanograms of nicotine per 1 milliliter of blood. In some preferred embodiments, the blood level of nicotine in the person after administration of the nicotine solution is from about 10 nanograms to about 50 nanograms of nicotine per 1 milliliter of blood. In a preferred embodiment, the nicotine solution is a nicotine suspension.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a diagrammatic representation of a frontal view of a nicotine delivery device of the invention that approximates the shape and size of a conventional drinking straw.

FIG. 2 is a diagrammatic representation of a frontal view of a nicotine delivery device of the invention that approximates the shape and size of a conventional cigarette.

DETAILED DESCRIPTION

The issued U.S. patents, published patent applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each were specifically and individually indicated to be incorporated by reference. Any inconsistency between these publications and the present disclosure shall be resolved in favor of the present disclosure.

The present invention provides smoking cessation methods and smoking cessation aids that deliver a nicotine solution through a tubular device to a user. The advantage of delivering nicotine through a tubular device is that the oral and tactile sensations experienced by the user approximate the ingrained hand-to-mouth behaviors associated with smoking. Thus, the device of the present invention offers the smoker oral and manual focus, which helps to alleviate cigarette cravings by providing an object for the smoker to manipulate and chew.

As shown in FIG. 1, the device of the invention may approximate a conventional drinking straw in size and shape. Alternatively, as shown in FIG. 2, the device may approximate a conventional cigarette in size and shape. The term "approximate" means that the device comprises an elongated tubular chamber **10**, with a first end **12** adapted for drawing in air or liquid from an external source and a second end **14** adapted for the application of oral suction, and that the dimensions of the device are similar to the dimensions of a conventional drinking straw or a conventional cigarette. In some preferred embodiments, as shown in FIG. 1, the device approximates a conventional drinking straw in shape and size. The chamber **10** is preferably from about 13 to about 20 centimeters long, with a diameter of from about 4 to about 8 millimeters. More preferably, the chamber **10** is from about 15 to about 17 centimeters long, with a diameter of from about 6 to about 7 millimeters. Alternatively, as shown in FIG. 2, the

device approximates a conventional cigarette in shape and size. In these embodiments, the chamber **10** is preferably from about 7 to about 11 centimeters long, with a diameter of from about 7 to about 10 millimeters. More preferably, the chamber **10** is from about 8 to about 10 centimeters long, with a diameter of about 8 millimeters. Examples of the tubular delivery devices of the present invention include, without limitation, devices such as those disclosed in U.S. Patent No. 5,718,681 (Manning) and U.S. Patent Nos. 5,780,058, 5,985,324, 5,989,590, 6,024,721, and 6,106,845 (Wong et al.).

Materials for making the tubular chamber **10** of the present invention may include, without limitation, paper, plastic such as propylene/styrene copolymers, polypropylene, high density polyethylene, low density polyethylene, ethylene vinyl acetate copolymer, and the like.

The tubular chamber **10** of the device of the present invention contains nicotine **16** that will be delivered to the user. The nicotine **16** may be in any useful form, such as levo nicotine, dextro nicotine, or a racemic mixture thereof. Pharmaceutically acceptable salt forms of nicotine are also suitable for use in the present invention. Nonlimiting examples of such suitable salt forms of nicotine include the dihydrochloride, sulfate, bitartrate, salicylate, hydrogen tartrate, and hemisulfate salts. Nicotine and its salt forms are commercially available, for example, from Sigma-Aldrich, St. Louis, MO.

Preferably, the nicotine **16** is a granulate. The term "granulate" means that the nicotine is in the form of a particulate such as grains or beads. The size of the grains or beads preferably is small enough not to be felt as separate particles in the mouth, preferably less than about 200 micrometers in diameter.

In some preferred embodiments, the nicotine granulate comprises particles of powdered nicotine which have been coated according to standard techniques known in the art (see, *e.g.*,

Deasy, Crit Rev. Ther. Drug Carrier Systems, **8**:39-89 (1991)). The term "powdered" means composed of fine particles. Glatt Air Technique (Ramsay, NJ) and Particle and Coating Technologies, Inc. (St. Louis, MO) provide particle coating services. Suitable coatings include, without limitation, hydroxy propyl cellulose, sugar, starch, polymer, resin, gum, wax, and fat. The diameter of the nicotine particles before coating is preferably less than about 200 micrometers, more preferably from about 20 to about 100 micrometers, and still more preferably from about 40 to about 60 micrometers.

In some preferred embodiments, the nicotine granulate comprises particles of powdered nicotine that are incorporated into microspheres, which may be coated as described above. Suitable materials for the microspheres include, without limitation, sugar, starch, acacia, sodium alginate, carbomer, cellulose, dextrotes, ethyl cellulose, methyl cellulose, povidone, and mixtures thereof. For example, the microspheres may comprise a degradable composition. The microspheres have a diameter of between about 300 micrometers and about 1000 micrometers, preferably between about 500 micrometers and about 600 micrometers. U.S. Patent No. 5,939,100 (Albrechtson et al.) discloses further examples of nicotine microspheres.

The coating on the nicotine particles or microspheres preferably is designed to mask the taste of the nicotine, and thus enhance palatability. Most preferably, the coating is formulated such that most, but not all, of the nicotine taste is masked. The advantage of such a formulation is that enough of the nicotine taste is masked that the nicotine particles are palatable, but enough nicotine taste remains that the user is aware that nicotine is being ingested. Thus, in some preferred embodiments, the formulation may comprise both coated and uncoated particles. The coating on the particles or microspheres also may be designed to achieve other functions, including, but not limited to, preventing clumping and preventing water absorption.

Preferably, a single dose of nicotine **16** from the device of the present invention contains a therapeutically effective amount of nicotine. The term "single dose" means the quantity of nicotine **16** provided in the chamber **10** and delivered to the user upon application of oral suction to the second end **14** of the chamber **10**. The term "therapeutically effective amount" means an amount sufficient to reduce a smoker's need for nicotine from burnt tobacco. This amount can be determined by the user's physician. An advantage of the smoking cessation devices of the invention is their ability to deliver a large dose of nicotine when necessary, or a smaller dose of nicotine when appropriate. Preferably, from about 1 milligram to about 40 milligrams of nicotine are provided by the device. Useful amounts include from about 1 milligram to about 5 milligrams, from about 4 milligrams to about 12 milligrams, from about 4 milligrams to about 20 milligrams, from about 5 milligrams to about 15 milligrams, from about 5 milligrams to about 20 milligrams, and from about 20 milligrams to about 40 milligrams of nicotine provided by the device in a single dose. A smoker attempting to stop smoking may use the device of the present invention from about 1 to about 12 times per day, preferably from about 5 to about 12 times per day, such that a total daily dose of from about 1 milligram to about 480 milligrams, preferably from about 5 milligrams to about 480 milligrams, of nicotine is delivered, depending on perceived need. Useful total daily doses include from about 1 milligram to about 60 milligrams, from about 4 milligrams to about 144 milligrams, from about 4 milligrams to about 240 milligrams, from about 5 milligrams to about 180 milligrams, from about 5 milligrams to about 240 milligrams, and from about 240 milligrams to about 480 milligrams of nicotine. The term "total daily dose" means the quantity of nicotine delivered to the user during a 24-hour period.

Such a dosing regimen preferably provides a blood level of nicotine of at least about 5 nanograms of nicotine per milliliter of blood, with a maximum peak of about 60 nanograms of

nicotine per milliliter of blood. Preferably, the blood level of nicotine in the user of the device is from about 10 nanograms to about 50 nanograms of nicotine per milliliter of blood. More preferably, the user's blood level of nicotine is about 20 nanograms of nicotine per milliliter of blood.

Blood levels of nicotine preferably may be measured by gas chromatography with nitrogen phosphorous detection as described, for example, by Jacob et al., J. Chromatography, **222**: 61-70 (1981). The dosing frequency may be adjusted so as to achieve a steady state concentration of nicotine in the blood. The steady state blood levels of nicotine preferably fall within the preferred blood level ranges described above. The quantities of nicotine described above are sufficient to deliver a therapeutically effective amount of nicotine into the user's metabolism, even after first-pass absorption by the liver. It will be understood by those skilled in the art that the preferred doses and blood levels of nicotine will vary according to the preferences, metabolism, and former smoking habits of the individual user of the smoking cessation aid of the present invention.

In one device encompassed by the present invention, the nicotine granulate is delivered to the user as a nicotine solution. The term "solution," as used herein, refers to a liquid into which the nicotine is dissolved, or a suspension or emulsion of nicotine in a liquid. Delivery of nicotine as a solution provides several advantages. Swallowing the solution provides the oral stimulation that smokers crave. However, the solution does not irritate the oral cavity as does nicotine gum. Additionally, nicotine in solution form is absorbed in the body more slowly than nicotine from a nasal spray. Such slow absorption allows for less frequent dosing and provides less potential for abuse. Finally, delivery of liquid along with the nicotine prevents high local concentrations of nicotine, which may result in cramping, for example, when a nicotine capsule is swallowed.

In some devices, the first end **12** of the chamber **10** is placed in contact with an external source of liquid and the user applies oral suction to the second end **14** of the chamber **10**. According to one method of the invention, a liquid is drawn into the first end **12** of the chamber **10** from the external source. The liquid then forms a suspension of the nicotine **16** granulate as it is drawn through the chamber **10**, and the suspension is delivered through the second end **14** of the chamber **10** into the user's mouth. Some or all of the nicotine **16** granulate also may dissolve in the liquid, such that the nicotine **16** is delivered as a solution. WO 99/55371 (Westman et al.) discloses non-limiting nicotine solutions whose properties may be desirable for use with the present invention.

The external source of liquid to be drawn into the tubular chamber **10** of a device of the invention is preferably a beverage. Most preferably, the beverage contains a flavoring, which helps to make the nicotine solution palatable. This is less crucial where the nicotine taste has already been masked by coating the particles of the nicotine granulate. The term "palatable" means that the taste of the solution is tolerable to the user. The beverage may comprise, but is not limited to, coffee, soda, sugar, fruit juice, carbonation, or ethyl alcohol, such as wine, beer, or hard liquor. Preferably, the beverage does not contain solids such as pulp. To be palatable, the nicotine solution preferably has an acidic pH. The term "acidic pH" means a pH of less than about 6.9. More preferably, the nicotine solution has a pH of less than about 5.5. Most preferably, the nicotine solution has a pH from about 2.0 to about 4.0. Flavorings such as coffee, alcohol, and fruit juice may be used to regulate the pH of the nicotine solution. For example, lime juice, cranberry juice, grapefruit juice, orange juice, tonic water, soda, and wine have pH's from about 2.0 to about 4.0, and beer, seltzer water, coffee, and have pH's less than about 6.9.

An advantage of the smoking cessation devices of the present invention is their compatibility with beverages that are acidic, as the majority of popular beverages are. Existing smoking cessation devices, such as nicotine gum and nicotine inhalers, may not be used in combination with acidic beverages because an alkaline environment is required for buccal absorption of the nicotine delivered by such devices. Acidic beverages must be avoided for a period of about one hour surrounding each use of a smoking cessation device relying on buccal absorption of nicotine. Thus, smokers attempting to use such devices to give up smoking must also avoid consuming a majority of beverages much of the time. In contrast, smokers using nicotine delivery devices of the invention, through which nicotine is orally ingested, may consume acidic beverages whenever they choose.

The tubular chamber **10** of the device of the present invention may comprise two or more lumens. The multiple lumens provide a plurality of smaller cross-sectional flow paths, which help to optimize the flow velocity and flow volume of the liquid from the external source, thus assuring rapid, uniform, and complete delivery of the nicotine **16** contained within the chamber **10**. The nicotine **16** may be contained in one of the lumens, or in multiple lumens. The multiple lumens may be of identical size or of different sizes.

Alternatively, the chamber **10** of the device of the present invention contains a pre-formulated solution of nicotine **16** such as, for example, a nicotine suspension. About 1 milliliter to about 40 milliliters of nicotine solution may be provided in the chamber. Preferably, from about 1 milliliter to about 10 milliliters, most preferably from about 1 milliliter to about 5 milliliters, of solution are provided. The preferred single doses of nicotine, total daily doses of nicotine, and nicotine blood levels are as described above for the nicotine granulate.

In another method of the invention, the user applies oral suction to the second end **14** of the chamber **10** of the device, such that a gas such as air is drawn through the first end **12** of the chamber **10** into the device. As the air is drawn into the chamber **10**, the nicotine **16** solution contained in the chamber **10** is delivered through the second end **14** of the chamber **10** into the user's mouth.

Alternatively, the user places the first end **12** of the chamber **10** in contact with an external source of a liquid and applies oral suction to the second end **14** of the chamber **10**, such that the liquid is drawn into the first end **12** of the chamber **10** from the external source. As the liquid is drawn through the chamber **10**, it is mixed with the solution of nicotine **16** contained in the chamber **10**, and the mixture is delivered through the second end **14** of the chamber **10** into the user's mouth. The external source of liquid is preferably a beverage, as described above for the device in which the chamber **10** contains a nicotine **16** granulate. Most preferably, the beverage comprises flavorings and pH ranges as described above.

The nicotine **16** solution contained within the chamber **10** may itself contain the flavorings described above. Preferably, the solution is pre-formulated to fall within the aforementioned pH levels through use of an acid such as, for example, carbonic acid, citric acid, acetic acid, tartaric acid, maleic acid, ascorbic acid, adipic acid, or combinations thereof. Such pre-formulation to optimize flavoring and pH is especially desirable if the user will be drawing air, rather than liquid, through the first end of the chamber, such that the nicotine **16** solution contained in the chamber **10** is delivered without any liquid from an external source that might enhance palatability.

The chamber **10** of the device of the present invention further contains a retainer **18** for preventing release of nicotine **16** from the first end **12** of the chamber **10**. The term "retainer"

refers to a disc, float, plug, or other restriction that blocks the diameter of the chamber **10** such that the nicotine **16** contained within the chamber **10** cannot be released from the first end **12** of the chamber **10**. The retainer **18** allows gas or liquid from an external source to enter the first end **12** of the chamber **10**, but prevents release of nicotine **16** from the first end **12** of the chamber **10**. The retainer **18** also discourages release from the first end **12** of the chamber **10** of liquid drawn into the chamber **10** from an external source or contained within the chamber **10** as part of a pre-formulated solution of nicotine **16**.

The retainer **18** may be fixed proximal to the first end **12** of the chamber **10**. "Proximal to" the first end **12** of the chamber **10** means toward or at the first end **12** of the chamber **10**. Alternatively, the retainer **18** may be transportable toward the second end **14** of the chamber **10**. For example, the retainer **18** is transported toward the second end **14** of the chamber **10** as the user applies oral suction to the second end **14** of the chamber **10**. Gas or liquid from an external source is drawn through the first end **12** of the chamber **10** into the device, and the nicotine **16** solution in the chamber **10** is delivered into the user's mouth. As it is drawn toward the second end **14** of the chamber **10** behind the nicotine **16** solution, the transportable retainer **18** assures that all of the nicotine **16** in the chamber **10** is cleanly delivered through the second end **14** of the chamber **10** into the user's mouth. The second end **14** of the chamber **10** is constructed such that the retainer **18** itself is blocked from entering the user's mouth. For example, the diameter at the second end **14** of the chamber **10** may be smaller than the diameter elsewhere in the chamber **10** and smaller than the diameter of the retainer **18**, such that the retainer **18** may pass from the first end **12** of the chamber **10** to the second end **14** of the chamber **10**, but cannot pass through the second end **14** of the chamber **10** into the user's mouth. The diameter at the second end **14** of the chamber **10** may be made smaller than the diameter elsewhere in the chamber **10** by a crimping

of the chamber **10**, a series of dimples in the circumference of the chamber **10**, or a continuous indentation in the circumference of the chamber **10** at the second end **14** of the chamber **10**. A transportable retainer **18** is particularly useful when the device is prefilled with liquid, *i.e.*, contains a pre-formulated solution of nicotine **16**.

The retainer **18** may comprise a restriction and a plug. The term "restriction" means that the diameter near the first end **12** of the chamber **10** is smaller than the diameter elsewhere in the chamber **10** and smaller than the diameter of the plug, such that the plug is contained within the chamber **10** and prevents release of nicotine **16** through the first end **12** of the chamber **10**. The restriction may result from, for example, a crimping of the chamber **10**, a series of dimples in the circumference of the chamber **10**, or a continuous indentation in the circumference of the chamber **10** near the first end **12** of the chamber **10**.

The retainer **18** may alternatively comprise a particle barrier with apertures or slits that allow liquid to pass through the barrier when oral suction is applied to the second end **14** of the chamber **10**. A cap may be placed over the first end **12** of the chamber **10** prior to use to avoid any possible loss of nicotine **16** or entry of contaminants through the particle barrier apertures or slits. The apertures must be small enough that nicotine **16** cannot pass through them and be released from the first end **12** of the chamber **10**. The slits are easier to manufacture and seal the chamber **10** more completely prior to use than the apertures do. Alternatively, the barrier is made from a material such as fine mesh or porous paper that will retain the nicotine **16** in the chamber **10** but requires no barrier apertures or slits to allow liquid to be drawn into the chamber **10**. For ease in construction, the barrier is preferably cone-shaped and located all the way at the first end **12** of the chamber **10**.

Alternatively, the retainer **18** comprises a one-way plug or valve. The plug or valve seals the first end **12** of the chamber **10** at atmospheric pressure. However, when suction is applied to the second end **14** of the chamber **10**, the plug is deformed and permits liquid from an external source to flow around the plug and into the chamber **10** through the first end **12** of the chamber **10**. The plug preferably has a density of less than one, such that it is drawn toward the second end **14** of the chamber **10** when suction is applied to the second end **14** of the chamber **10** and the nicotine **16** contained within the chamber **10** is delivered into the mouth of the user. When suction is removed from the second end **14** of the chamber **10**, the plug relaxes, seals the chamber **10**, and remains stationary. Transportation of the plug all the way to the second end **14** of the chamber **10** indicates that the entire dose of nicotine **16** contained within the chamber **10** has been delivered.

The retainer **18** alternatively comprises a cylindrical body with at least one protrusion on its exterior surface. Liquid from an external source is drawn through or around the retainer **18** and into the chamber **10**, but the protrusions prevent nicotine **16** solution from leaking through or around the sides of the retainer **18** and out of the first end **12** of the chamber **10**. The protrusions are fins, ridges, or rings which act as a seal for the chamber **10** and also create friction or drag between the retainer **18** and the chamber **10**, which allows time for the liquid from the external source to mix with the nicotine **16** after passing through or around the retainer **18**.

The retainer **18** of the present invention may be made from, for example, thermoplastic materials or low or high density foam materials such as, without limitation, ethylene vinyl acetate copolymers, polyolefins such as polyethylene, polypropylene, and the like, or closed cell foam. Alternatively, the retainer **18** may comprise, for example, a compressible plug of bonded fibers. The fibers may be polymeric fibers, such as polyolefin fibers with or without a polyester

core, polyester, cellulose acetate, nylon, felt, or cotton. The uncompressed fiber plug preferably has a diameter slightly larger than the diameter of the chamber **10**. Thus, after insertion in the chamber **10**, the plug seals and prevents the release of nicotine **16** from the chamber **10**, but still allows liquid to be drawn into the chamber **10** when oral suction is applied to the second end **14** of the chamber **10**.

In some embodiments, the chamber **10** of the device of the present invention preferably also contains a removable end cap **20** or seal located at the second end **14** of the chamber **10**. The removable end cap **20** or seal prevents the nicotine **16** granulate or pre-formulated nicotine **16** solution contained within the chamber **10** from being released through the second end **14** of the chamber **10** during shipping and storage of the device. Before using the device, the user removes the end cap **20** or seal from the second end **14** of the chamber **10** so that the nicotine **16** granulate or pre-formulated nicotine **16** solution contained within the chamber **10** may be delivered through the second end **14** of the chamber **10** into the user's mouth. Materials for making the end cap **20** or seal of the present invention may include, without limitation, paper, foil, plastic such as propylene/styrene copolymers, polypropylene, high density polyethylene, low density polyethylene, ethylene vinyl acetate copolymer, and the like.

In some instances, the device, itself, may comprise a flavoring, such that it tastes pleasant for chewing as, before, or after the nicotine dose has been delivered. The flavoring may be, for example, sugar, cinnamon, spearmint, peppermint, wintergreen, bubble gum, fruit, chocolate, anise, nut, coffee, tobacco, or combinations thereof. Preferably, the flavoring is selected from the group consisting of spearmint, peppermint, wintergreen, and cinnamon.

The device as described in detail above provides the novel synergistic combination of oral and tactile stimulation along with a controlled dose of nicotine in non-irritating solution

form. Smokers attempting to stop smoking may use the device as an aid that can satisfy nicotine needs and at the same time prevent cigarette cravings by providing a substitute for the hand-to-mouth behavioral component of smoking. The synergistic combination of the present invention provides an important new method for reducing the incidence of tobacco smoking in smokers who appreciate the health risks of smoking and wish to stop.

The following nonlimiting examples further illustrate certain preferred embodiments of the present invention:

EXAMPLE 1: Safety and Pharmacokinetics Study

1. Device

Nicotine is administered orally using a straw-like smoking cessation device of the invention as shown in FIG. 1. The chamber **10** is a plastic drinking straw. The retainer **18** is a filter at the first end **12** of the straw. The user places the first end **12** of the device in a glass of apple juice and applies oral suction to the second end **14** of the device, such that the juice and nicotine **16** are delivered into the user's mouth.

The nicotine **16** in the device is in the form of coated sugar spheres of nicotine bitartrate having a diameter of approximately 500 micrometers. The nicotine spheres are prepared by spraying nicotine bitartrate dihydrate with a binder onto sugar spheres and applying a film coating. Using a Wurster processing unit, particles are suspended in air using a controlled airflow system and a coating suspension is added at a controlled rate via a pneumatically atomized nozzle. As atomized droplets of the coating solution contact the particles, they spread and coalesce on the particle surface. Excess moisture from the applied liquid evaporates in the apparatus, leaving a coated dry substance. Mixing of the coating suspension occurs throughout the manufacturing process to ensure uniformity of the suspension.

2. Administration

On day one, following overnight abstinence from smoking, healthy adult smokers who wish to give up smoking receive a single dose of nicotine or placebo. Smokers are assigned to each dosage group in a double blind, randomized manner, as is well known in the art. The following data are collected before dosing, every thirty minutes for the first two hours after dosing, and every hour for the following six hours: plasma levels of nicotine and cotinine, vital signs, adverse events, and patient's assessment of cigarette cravings. Baseline and endpoint clinical chemistry, hematology, urinalysis, and ECG are also monitored.

On day eight, again following overnight abstinence from smoking, the same subjects receive the same dose of nicotine or placebo. The dose is repeated periodically throughout the day. The following data are collected as described above before the first dosing and one hour after each dose is administered: plasma levels of nicotine and cotinine, vital signs, adverse events, and patient's assessment of cigarette cravings. Baseline and endpoint clinical chemistry, hematology, urinalysis, and ECG are also monitored. The data are used to evaluate the safety and pharmacokinetics of nicotine delivery by the smoking cessation device.

EXAMPLE 2: Efficacy Study

In a double blind study, three hundred healthy adult smokers who wish to give up smoking use the smoking cessation device as described in Example 1 to deliver nicotine or placebo over a ten week period. Each device contains 5-10 mg of nicotine or placebo. Subjects are instructed to use the device as needed for smoking urges, but not to exceed 12 doses per day. Patients are concurrently enrolled in a counseling program to provide behavioral support for smoking cessation. Smoking abstinence data are collected during the last eight weeks of treatment, serving as the primary endpoint. Abstinence is defined as four weeks of continuous

abstinence from smoking during the study period. Subjects have weekly clinic visits for monitoring plasma levels of nicotine and cotinine, vital signs, adverse events, and patient's assessment of cigarette cravings. Baseline and endpoint clinical chemistry, hematology, urinalysis, and ECG are also monitored.

EQUIVALENTS

While the foregoing invention has been described in some detail for purposes of clarity and understanding, it will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the scope of the invention and the attached claims.